Annals of Clinical and Analytical Medicine
Original Research

Platelet large cell ratio and immature granulocyte values in pelvic inflammatory disease

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Abstract

Aim: Pelvic inflammatory disease (PID) affects 4% of women of reproductive age and can lead to complications such as pelvic pain, ectopic pregnancy and infertility. Our study aimed to compare the Platelet Large Cell Ratio (PLCR) and percentage of immature granulocytes (%IG) results in PID and control groups and determine their significance for diagnosis, also to evaluate the association between early detection and severity of PID and parametric values such as length of hospital stay and duration of antibiotic treatment.

Material and Methods: In our retrospective case-control study, we retrospectively analyzed data of patients who presented to the Emergency Room of Gynecology and Obstetrics Department of Istanbul Teaching and Research Hospital with lower quadrant tenderness and/or fever and were admitted to the ward with a diagnosis of PID between January 2018 and January 2019. PID diagnosis was made using the criteria of " Sexually Transmitted Diseases Treatment Guidelines, 2015". PLCR and %IG values were calculated with semiconductor flow cytometry.

Results: A statistically significant difference was observed between groups in %IG, leukocyte count, CRP and blood sedimentation values ($p < 0.05$). While a high correlation was found between %IG value and length of hospital stay, no correlation was found with the PLCR value. A cut-off value of 0.35 %IG showed a high sensitivity of 73% and specificity of 78% for PID diagnosis (AUC:0.81).

Discussion: Our study is one of the first to investigate PLCR and %IG value in patients with gynecological infections. Our study showed that the %IG value has a high differential diagnostic value, especially in PID patients, even in patients whose conventional infection markers were not elevated at the time of initial hospital admission.

Keywords

Pelvic Inflammatory Disease, PLCR, %IG

DOI: 10.4328/ACAM.20926 Received: 2021-10-29 Accepted: 2021-11-14 Published Online: 2021-11-17 Printed: 2022-04-01 Ann Clin Anal Med 2022;13(4):360-364
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Introduction

Pelvic Inflammatory Disease (PID) is a sexually transmitted infection that affects 4% of women of reproductive age and causes complications such as pelvic pain, ectopic pregnancy and infertility [1-3].

Clinicians should use the diagnostic criteria for PID recommended by the Centers for Disease Control and Prevention (CDC) [2]. Barrier contraception methods appear to be protective [4,5], and their combination with first-line antibiotics has a high success rate [6]; in new studies, attempts are made to identify markers associated with conservative treatment failure to maximize timely treatment and avoid delays in surgical treatment [7]. Repeated episodes of PID have been found to increase morbidity and worsen fertility outcomes [8, 9].

Diagnostic biomarkers have been successfully used in various fields of medicine. However, timely diagnosis of bacterial infections remains a challenge. The earlier this treatment-delaying process is detected, the sooner additional preventive and potentially curative measures can be taken.

Platelet Large Cell Ratio (PLCR) reflects the proportion of platelets larger than 12 fL (the normal value for PLCR is 30% of the total platelet count). Large platelets are usually younger and contain more intracellular granules. Therefore, they have a higher thrombogenic potential [10, 11]. It is known that PLCR is mainly related to mean platelet volume (MPV), but is more sensitive to changes in platelet size. In support of this information, Babu et al. showed that PLCR value inversely correlates with platelet count and directly correlates with MPV and helps in the differential diagnosis of thrombocytopenia [12].

Despite the availability of immature granulocyte (IG) measurement, it is not yet used as a routine diagnostic tool in infected patients. Next-generation analyzers are now capable of automatically and very accurately determining the actual IG count and percentage in peripheral blood samples [13]. The performance of IG measurement remains uncertain compared with conventional infection markers such as white blood cell (WBC) count, absolute neutrophil count (ANC), and C-reactive protein (CRP).

Our study aimed to evaluate the results of PLCR and %IG in patients with pelvic infections such as tuba-ovarian abscess and endometritis in comparison between PID and control groups, to determine their significance in diagnosis and also to investigate whether they can be used as a cost-effective and rapid inflammatory marker to assess the relationship between early detection and severity of PID and parametric values such as length of hospital stay and duration of antibiotic treatment.

Material and Methods

In our retrospective case-control study, we retrospectively analyzed data of patients who presented to the Emergency Room of Gynecology and Obstetrics Department of Istanbul hospital with lower quadrant discomfort and/or fever and were admitted to the ward with a diagnosis of PID between January 2018 and January 2019. PID diagnosis, after exclusion of other diseases, was made using the 'Sexually Transmitted Diseases Treatment Guidelines, 2015' [2] diagnostic criteria in conjunction with one of the following major criteria and at least one of the minor criteria: Major criteria: Cervical motion tenderness on bimanual examination, tenderness over the uterus, tenderness of bilateral adnexa.

Minor criteria: Fever>38,3°C, abnormal cervical or vaginal discharge, elevated erythrocyte sedimentation rate (ESR), elevated C-reactive protein (CRP), laboratory findings of Neisseria gonorrhoeae and Chlamydia trachomatis infection of the cervix, increased leukocyte count on microscopic examination of the vaginal swab.

Exclusion criteria were defined as follows: severe trauma, infection immediately after surgery, cardiac shock, patients on immunotherapy, autoimmune disease, paraneoplastic syndrome, acute graft-versus-host disease.

A complete blood count (CBC) was requested when PID was suspected after taking a clinical history and administering physical therapy to patients presenting to the emergency room with complaints of acute abdominal pain and/or tenderness. Leukocyte count, neutrophil count, lymphocyte count, PLCR, and %IG were measured with an automated hematology analyzer (XN-1000; SysmexCorp.) from blood samples collected at the initial admission to the emergency room before hospitalization. Using data obtained from CBC analysis, PLCR and %IG values were calculated by semiconductor flow cytometry.

All patients who were submitted to our inpatient service received cefoxitin (2 g) parenterally every 6 hours and doxycycline (100 mg) parenterally twice a day for a minimal 48-hour admission, patients transitioned from parenteral to oral therapy after 48 hours of clinical improvement, followed by doxycycline (100 mg) orally twice a day for a total 14-day course.

The study patients were divided into two groups to compare the PLCR and %IG results: the PID group consisted of patients with PID diagnosis and the control group. The control group consisted of healthy women admitted to the Obstetric and Gynecological outpatient clinics of Istanbul Training and Research Hospital for routine gynecologic follow-up purposes, matched for age and BMI, and with no suspicion of PID and/or disease.

Our study was approved by the Ethics Committee of Istanbul hospital dated 07/02/2020 (Decision no: 2173). As our study is retrospective, informed consent could not be obtained from the patients.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation, and categorical data as numbers and percentages. For intergroup analysis of continuous variables, normality analyzes were performed using the Kolmogorov-Smirnov Goodness of Fit Test. Receiver Operator Characteristics Curve (ROC) analysis was performed to determine the success of the inflammatory marker %IG in predicting PID. Continuous variables were expressed as mean ± standard deviation, categorical data as numbers and percentages. Pearson correlation analysis was performed for correlation using length of hospital stay, CRP, duration of antibiotic use and s ESR as dependent variables and PLCR and %IG values as independent variables. Statistical significance was taken as <0.05 and SPSS 13 version was used for calculations.

Results

In Table 1, no statistically significant difference was found

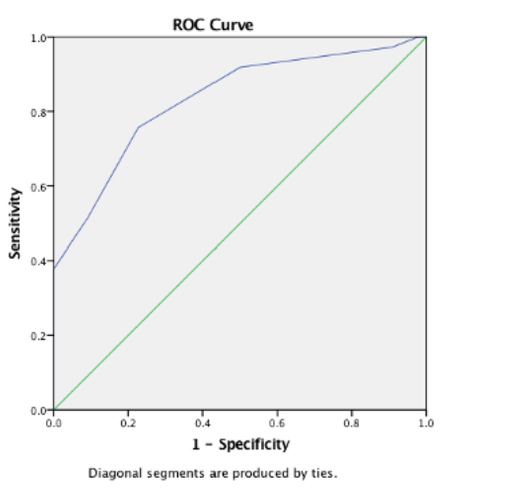

Figure 1. ROC Curve of %IG value for PID diagnosis
*%IG: Percent Immature Granulocyte

Table 1. Biochemical and demographic data of PID and control groups

	PID group (n: 42)	Control group (n: 44)	P-value
	(mean± SD)	(mean± SD)	
Age (year)	38.2±10.4	36.3±5.2	P=0.025*
BMI (height/kg2)	25.57±5.5	26.3±6.4	P=0.034*
PLCR	24.81±7.5	28.24±8.5	P=0.069
%IG	0.53±0.33	0.27±0.11	P=0.000*
Leukocyte count (x 109/L)	14.76±6.06	7.00±3.3	P=0.00*
ESR	69.3±6.7		
CRP (mg/L)	154.2±3.5		

* Independent sample T-Test, *PID: Pelvic Inflammatory Disease, BMI: Body Mass Index, PLCR: Platelet Large Cell Ratio, %IG: Percent Immature Granulocyte, ESR: Erythrocyte Sedimentation Rate, CRP: C-Reactive Protein.

Table 2. Correlation of PLCR and %IG values with clinical and laboratory data

	1	2	3	4	5	6
1 CRP						
2 ESR	.34					
	.07					
	29.00					
3 Leukocyte count	.21 -.20					
	.20	.30				
	39.00	29.00				
4 The length of hospital stay	.23	.48**	.14			
	.15	.01	.37			
	39.00	29.00	42.00			
5 Duration of antibiotic use	.17	.46*	.03			
	.29	.01	.85	.00		
	39.00	29.00	42.00	42.00		
6 PLCR	.19	.14	-.17	.05		
	.26	.51	.32	.78	.43	
	35.00	25.00	38.00	38.00	38.00	
7 IG %	.43**	.10	.47**	.50**	.29	
	.01	.63	.00	.00	.07	.66
	35.00	25.00	38.00	38.00	38.00	38.00

PLCR: Platelet Large Cell Ratio, %IG: Percent Immature Granulocyte, ESR: Erythrocyte Sedimentation Rate, CRP: C-Reactive Protein. ** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).

between age and BMI values in PID and control groups (p >0.05). A statistically significant difference was found between the groups in %IG, leukocyte values (p <0.05). The mean %IG value for PID patients was 0.53 and the mean PLCR value was 24.82. Although the PLCR value was lower than that of control patients, no statistical significance was reached.

In Figure 1, the ROC curve for PID and control groups showed a sensitivity of 73% and a specificity of 78% for PID diagnosis with a cut-off value of 0.35 for %IG (AUC:0.833). (Asymptotic 95% Confidence Interval, lower limit: 0.255, upper limit: 0.500).

In correlation analysis, although %IG values were positively correlated with length of hospital stay, CRP and leukocyte count (r=0.50), no correlation was found with prognostic factors such as duration of antibiotic use, leukocyte count, CRP values and PLCR values. A positive correlation was found between ESR and length of hospital stay and duration of antibiotic use (r=0.49, r=0.46) (Table 2).

Tubal-ovarian abscess (TOA) was found in 18 out of 42 PID patients (42%).

A complete blood count obtained during hospitalization showed leukocytosis (WBC 10.2 x 109/L) in 21 of 42 patients (50%).

Elevated CRP was found in 22 of 42 patients (50%) in the CBC taken during hospitalization (CRP >5 mg/L).

Blood culture results were positive in 8 of 42 PID patients (19%); E.coli grew in 4 patients, Streptococcus agalactia in 2 patients, and Staphylococcus epidermidis in 2 patients.

Discussion

The absence of the classic risk factors for PID and the triad of cervical, uterine or adnexal tenderness does not exclude the diagnosis of PID and TOA. Although PID is rare in perimenopausal women, it is critical to consider the diagnosis in differential diagnosis and to recognize it early. Clinical diagnosis of PID is often challenging, even for the most experienced clinicians.

The Centers for Disease Control and Preventation has highlighted this fact in its current guidelines; clinical diagnosis of PID has a positive predictive value between 65% and 90% [2]. This means that clinicians misdiagnose one in three patients. The reason for the low clinical diagnosis is that many adjacent organs (urinary tract, gastrointestinal tract, musculoskeletal system, etc.) have symptoms that mimic PID. No physical findings, imaging techniques, or serologic markers have high specificity and sensitivity for PID diagnosis.

The vast majority of women with tubal factor infertility do not have a history of PID, indicating the prevalence of subclinical, undiagnosed infection. Sweet estimates that approximately 60% of PID are subclinical, 36% are mild to moderate, and the remaining 4% are severe [14].

Despite all the advances in diagnostic and treatment methods, there are still cases of ruptured TOA, resulting in a mortality rate of 5 to 10% [15], if not diagnosed and treated in time, it can lead to bacteremia, septicemia, or septic shock.

The number of studies on PLCR is still limited. In a recent study consistent with our data, PLCR was detected to be statistically significantly lower (p <0.03) in patients with active periodontitis than in the control group [16]. We hypothesize that this is caused by large platelets that are destroyed during infection.

In our study, no correlation was found between PLCR values and

length of hospital stay and duration of antibiotic use. Gao Y. et al. in their study, in contrast to our study, reported increased PLCR values with the severity of sepsis in patients with septic shock, but since there was no control group in their study, no correlation with the patient group was reported [17]. The fact that the patient population in their study was more critical than our patient group may explain the correlation with the severity of infection.

Our study is the first to report a %IG cutoff value for the diagnosis of PID. Some recent studies have investigated the role of percent IG measurement as a potential marker for predicting the severity of infection [18, 19]. However, these studies mainly focused on critically ill adult patients in intensive care units. Only one study examined % IG in a general outpatient setting that included all age groups, including pediatric, obstetric, and geriatric populations [19]. Nierhaus et al. found that the %IG value significantly distinguished infected patients from uninfected patients with a sensitivity of 89.2% and a specificity of 76.4%, especially in the first 48 hours after systemic inflammatory response syndrome (SIRS). The %IG value was more valuable than other clinical parameters such as CRP, lipopolysaccharide-binding protein, and interleukin 6. In their study, %IG showed a higher positive predictive value for SIRS than other parameters during the first five days of SIRS [18]. In another recent study conducted in the SIRS population, %IG at <2.0% value excluded the diagnosis of sepsis with a specificity of 90.9% [19].

Van der Geest et al. observed that WBC and CRP had comparable predictive power as %IG for microbial infections. However, they showed that %IG excluded infection at an early stage. In agreement with our study, it has been reported that %IG greater than 3% has a high sensitivity and is an indicator of sepsis risk [20]. In our study, only 50% of patients with PID had elevated CRP and WBC levels in the blood drawn at initial hospital admission. These results draw attention to the fact that %IG is a marker that increases in the early period, in line with previous studies [19,20].

Although blood culture is still considered the gold standard for diagnosing bacteremia and sepsis, only one-third of patients presenting with clinical features of sepsis have a positive blood culture, with a long incubation period for the detection of microorganisms [19]. In recent years, several publications have shown the association between blood culture results and %IG values [19, 21]. Both studies [20, 21] revealed the correlation of blood culture positivity with %IG value, and one study revealed that %IG value has equivalent utility to procalcitonin and CRP in distinguishing true bacteremia from contamination in culture-positive patients [21]. Similarly, in our study, only 19% of PID patients had positive blood culture results. The results of our two culture-positive patients were due to contamination. Due to the insufficient number of our culture-positive patients, statistical analysis with %IG values could not be performed.

No correlation was determined between duration of antibiotic use and %IG values in our study, but a high correlation was determined between the length of hospital stay and %IG values. The duration of antibiotic use depends on the approach of different clinicians. There are very few publications on the association of %IG values with disease prognosis. In a single-center study conducted in 2015, an association with diffuse intravascular coagulation was found only for %IG value and lactate when distinguishing complicated from uncomplicated sepsis and in subgroup analyzes [22]. However, in the study by Park et al., elevated %IG was detected to be insufficient to differentiate between complicated and uncomplicated sepsis in their patients [23]. We hypothesize that the %IG value, which we found to be significant for the prognosis of PID patients, may contribute to the establishment of a standardized treatment model for these patients.

According to the results of our study, it was concluded that after %IG value, the ESR value also provided valuable data on PID prognosis according to conventional inflammatory markers. ESR is not recommended as a screening test in asymptomatic patients, but only as a supportive diagnostic test in symptomatic patients because it is influenced by several factors and has low sensitivity and specificity [24]. We think that the ESR value, a minor marker in PID diagnosis, together with %IG value may contribute to the duration and dose adjustment of antibiotic treatment.

Conclusions

Nowadays, the diagnosis of PID is based on conventional markers and culture-based pathogen detection, which are non-specific and have low sensitivity and specificity, especially in the early stages of the disease. This can lead to diagnostic uncertainty, delayed and/or overuse of antibiotics, and failure to identify women who might benefit from treatment, particularly those with subclinical infections. Our study is one of the first to investigate PLCR and %IG values in patients with gynecologic infections. We found that %IG value is an objective inflammatory marker that can be used for early diagnosis of PID, is simple and rapid, and does not waste time, especially in patients whose conventional infection markers are not yet elevated.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: *None*

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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How to cite this article:
Nil Atakul, Berna Sermin Kılıc. Platelet large cell ratio and immature granulocyte values in pelvic inflammatory disease. *Ann Clin Anal Med 2022;13(4):360-364*